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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/643,141	08/18/2003	Stephen L. Hutcherson	C01037.70049.US	3287

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EXAMINER	
GUSSOW, ANNE	

ART UNIT	PAPER NUMBER
1643	

MAIL DATE	DELIVERY MODE
11/07/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/643,141	HUTCHERSON ET AL.	
	Examiner	Art Unit	
	ANNE M. GUSSOW	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 August 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26-48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/14/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 14, 2008 has been entered.

2. No claims have been amended, canceled or added.

   Claims 26-48 are under examination.

3. The following Office Action contains NEW GROUNDS of Rejection.

Information Disclosure Statement

4. The information disclosure statement (IDS) submitted on August 14, 2008 has been fully considered by the examiner and an initialed copy of the IDS is included with the mailing of this Office Action.

Objections Maintained

5. The objection to the specification as failing to provide antecedent basis for the phrase "wherein the phosphorothioate oligonucleotide is not antisense" is maintained.

The response filed August 14, 2008 has been carefully considered but is deemed not to be persuasive. The response states that, when the specification provides a teaching that the oligonucleotide may have antisense activity, it is implied that it may not have antisense activity. If the oligonucleotide does not have antisense activity it is not an antisense oligonucleotide. Antisense oligonucleotides function by binding to a complementary RNA sequence and preventing production of a protein. The function of antisense oligonucleotides is dictated by the structure. The primary structure of an antisense oligonucleotide, the nucleotide sequence, determines whether the oligonucleotide is complementary to an RNA. The fact that applicant has taught in the specification that the oligonucleotides can work independent of an antisense method, clarifies that the invention is not limited to antisense oligonucleotides (see response pages 8-9).

In response to this argument applicant's description of the oligonucleotides as claimed is limited to the structure of the molecule, both antisense and not antisense describe structural characteristics of the molecule. The argument presented by applicant describes the function of the molecule as not having an antisense effect. As claimed, the function of the molecule is to stimulate an immune response. The specification describes the oligonucleotides as being antisense molecules (see page 10 lines 16-18 of the as-filed specification and the previous office action). Thus, the

structure of the molecule as disclosed is antisense, but the structure of the molecule as claimed is not antisense.

Therefore after a fresh consideration of the claims and the evidence provided the objection is maintained.

Rejections Maintained/NEW GROUNDS of Rejection

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. The rejection of claims 26-48 under 35 U.S.C. 112, first paragraph, as lacking written description is maintained.

The response filed August 14, 2008 has been carefully considered but is deemed not to be persuasive. The response states that one objective of the written description requirement is "to put the public in possession of what the applicant claims as the invention". MPEP 2163(I). Applicant has met this objective by disclosing the structure and function of the claimed genus of immunopotentiating oligonucleotides. The public was already in possession of phosphorothioate containing oligonucleotides. Applicant has taught in the specification that such oligonucleotides, regardless of their ability to produce antisense effects are useful for promoting cell mediated and local immune responses. Accordingly, the written description requirement for the claimed methods is

met in view of the teaching in the specification and that which was already known in the art at the time of filing relating to oligonucleotides (see response page 5).

In response to this argument, applicant has described specific oligonucleotides (table 1, page 17, page 10 lines 16-20, and page 12 lines 1-9) that are disclosed to be antisense molecules. Applicant's statements that the public was in possession of phosphorothioate containing oligonucleotides are not persuasive because one of ordinary skill in the art would not expect all possible phosphorothioate analogs, or even a representative number, to induce cell mediated or local immune responses. Additionally, the oligonucleotide species disclosed in applicant's specification are antisense molecules while the claims are drawn to molecules that are not antisense.

The written description of the present application only sets forth antisense oligonucleotides that stimulate an immune response, however, the claims encompass thousands of immunostimulatory oligonucleotides that differ in length and sequence, and which generate an immune response. The structures of the immunostimulatory oligonucleotides that generate an immune response are not known and the genus is inclusive to a variety of subgenera having disparate structures and functions. Thus, the instant disclosure does not provide sufficient written description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus

of immunostimulatory oligonucleotides that generate an immune response. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. The disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure "indicates that the patentee has invented species sufficient to constitute the gen[us]. " See *Enzo Biochem*, 323 F.3d at 966, 63 USPQ2d at 1615; *Noelle v. Lederman*, 355 F.3d 1343, 1350, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) (Fed. Cir. 2004)("[A] patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated."). "A patentee will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a single species when ... the evidence indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed." For example, Ratajczak et al. (Proc. Natl. Acad. Sci. USA 89:11823-11827, 1992, of record) teach the administration of sequence specific sense, antisense, and control phosphorothioate oligonucleotides to mice result in different responses depending on the sequence administered, see page 11825, left column, third full paragraph, lines 16-27. It cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. *In re Smith* 173 USPQ 679, 683 (CCPA 1972).

Further, it is not sufficient to define a substance solely by its principal biological property, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property. Per the *Enzo* court's example, (*Enzo Biochem, Inc. v. Gen-Probe Inc.*, 63 USPQ2d 1609 (CA FC 2002) at 1616) of a description of an anti-inflammatory steroid, i.e., a steroid (a generic structural term) couched "in terms of its function of lessening inflammation of tissues" which, the court stated, "fails to distinguish any steroid from others having the same activity or function". Similarly, the function of generating an immune response or being "not antisense" does not distinguish any oligonucleotide having immunostimulatory functions from others having the same activity or function and as such, fails to satisfy the written-description requirement. Applicant has not disclosed any relevant, identifying characteristics, such as structure or other physical and/or chemical properties, sufficient to show possession of the claimed genus. Mere idea or function is insufficient for written description; isolation and characterization at a minimum are required. A description of what a material does, rather than what it is, usually does not suffice. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed

above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of not antisense oligonucleotides that generate an immune response, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddles v.Baird*, 30 USPQ2d 1481, 1483. In *Fiddles v. Baird*, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Applicant is reminded that the written description requirement is separate and distinct from the enablement requirement. *In re Barker*, 559 F.2d 588, 194 USPQ 470 (CCPA 1977), cert. denied, 434 U.S. 1064 (1978); *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1562, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991). Applicant was not in possession of the broad genus of oligonucleotides that are encompassed by not antisense since the disclosure describes antisense molecules.

Therefore after a fresh consideration of the claims and the evidence provided the rejection is maintained.

8. The rejection of claims 26-48 under 35 U.S.C. 112, first paragraph, as lacking enablement is maintained.

The response filed August 14, 2008 has been carefully considered but is deemed not to be persuasive. The response states that the Examiner has dismissed Applicant's arguments in response to Crooke et al because seven additional references had been cited in prior office actions to support the state of the art regarding phosphorothioate analogs and that not all phosphorothioate analogs are immunostimulatory. However, Applicant had previously addressed each of these references. The references were not mentioned in the last office action and were thus not addressed again by Applicant. Applicant hereby addresses these references below... (see response pages 5-8).

In response to this argument, the examiner addressed only the Crooke, et al. reference in the February 15, 2008 office action because arguments regarding the other references had been made on the record in the October 17, 2006 office action. The references have been considered together, in addition to applicant's arguments, and the evidence provided in the specification regarding the enablement of the claimed invention.

The specification discloses producing an immune response by administering only *one antisense* phosphorothioate, ISIS 2105 in rats (Example 7, pages 23-24), mice (Example 8, pages 24-25), and in humans (Examples 9-11, pages 25-26). Thus, the data provided is not commensurate in scope with the claims which are drawn to

methods of stimulating an immune response using any phosphorothioate oligonucleotide analogs which are not antisense.

The arguments from the October 17, 2006 office action are repeated below.

Applicants further argue the references cited by the Examiner to demonstrate the state of the art and the level of unpredictability in the art. For example, Applicants argue that Allison et al. (Molecular Immunology 28: 279-284, 1991) cited by the Examiner shows the traditional way an immune response is evaluated which is by measuring antibody types and levels. Applicants argue that the instant specification demonstrates the efficacy of the phosphorothioate oligonucleotides in both antibody production and cytokine production in the Examples, see Remarks, page 8, third full paragraph, lines 12-16. The Examiner does not concur. The specification demonstrates an immune response by administering only one antisense phosphorothioate, ISIS 2105 in rats (Example 7, pages 23 and 24) and mice (Example 8, pages 24 and 25) and humans (Examples 9-11, pages 25 and 26). Thus, the data provided in the specification is not commensurate in scope with the claims, which are drawn to methods of stimulating an immune response using any phosphorothioate oligonucleotide analogs.

Applicants argue that the three references cited by the Examiner as evidence that "induction of splenomegaly and stimulation of B-lymphocyte proliferation in mice injected with phosphorothioate oligos occurs unpredictably in a manner that is dependent on the nucleotide sequence of the phosphorothioate oligonucleotide analogs" does not support the Examiners' broad conclusion that this was known or widely accepted in the art at the time the instant application was filed and that "each of

these references represents a very small number of examples and the effects may be explained by antisense activity," see Remarks, page 9, lines 5-9. The Examiner does not concur. Ratajczak et al. (Proc. Natl. Acad. Sci. USA 89:11823-11827, 1992) teach the administration of sequence specific sense, antisense, and control phosphorothioate oligonucleotides to mice result in different responses depending on the sequence administered, see page 11825, left column, third full paragraph, lines 16-27.

In response to the Vollmer et al. (Antisense and Nucleic Acid Drug Development 12: 165-175, 2002) reference, Applicants argue that the results are dosage specific and that the data highlighted by the Examiner in figure 2 corresponds to a single dose with no indication of that being the optimal dose. Applicants argue that the McCluskie et al. (Vaccine 19: 2657-2660, 2001) and Jones et al. (Vaccine 17: 3065-3071, 1999) references similarly demonstrate that higher doses may be necessary for an immune response and not that phosphorothioate nucleotide analogs are not immunostimulatory. In response, the Examiner cited the art listed above to demonstrate that administering any phosphorothioate oligonucleotide is unpredictable. These teachings combined with the fact that Applicants have not provided sufficient evidence in the disclosure would lead one of ordinary skill in the art to conclude that administering any phosphorothioate oligonucleotide analog to stimulate an immune response is unpredictable. Again, the Examiner points out that the data provided in the specification is limited to only one species of phosphorothioate oligonucleotide, ISIS 2105, and is not sufficient to provide enablement for the entire genus of phosphorothioate analogs given the teachings of Vollmer et al., Ratajczak et al., as well as Mojcik et al., Branda et al., and McIntyre et al.

Lastly, Applicants argue that the specification must be enabled as of the filing date. Applicants argue that since the effective filing date of the instant application is March 25, 1994 requires consideration of what was known at the time of filing and that "publications dated after the filing date providing information publicly disclosed after the filing date cannot be used to show what was known at the time of filing, see Remarks, page 10, 2nd full paragraph, lines 1-10. The Examiner does not concur. While it is true that publications dated after the filing date providing information publicly first disclosed after the filing date generally cannot be used to show what was known at the time of filing, post filing art can be used to support an Examiner's position of unpredictability so that a person skilled in the art would not have believed that the success with one specific species, in this case one specific phosphorothioate oligonucleotide sequence, could be extrapolated successfully to all phosphorothioate oligonucleotide sequences, see MPEP § 2164.05(a) [R-2], last paragraph and In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513-1514 (Fed. Cir. 1993) (See October 17, 2006 Office Action pages 5-8).

Therefore, one of ordinary skill in the art would conclude that methods of eliciting an immune response by the administration of any phosphorothioate oligonucleotide analog which is not antisense would require undue experimentation in order to use the invention as claimed by the Applicants.

9. Claims 26-48 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for stimulating an immune response by administering an ISIS 2105 antisense phosphorothioate oligonucleotide analog by

intradermal administration, does not reasonably provide enablement for stimulating an immune response with just any phosphorothioate oligonucleotide that is not antisense by just any route of administration. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in In re Wands, 8 USPQ2d 1400 (CAFC 1988).

> Wands states on page 1404,
> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The claims are broadly drawn to a method for stimulating an immune response in a human comprising administering by a route selected from the group consisting of inhalation, opthamalic, intranasal, parenteral, oral and intradermal to the human as an immunopotentiator an amount of a phosphorothioate oligonucleotide analog effective to stimulate a cell-mediated immune response, wherein the phosphorothioate oligonucleotide analog is not antisense.

The specification discloses intradermal administration of an antisense phosphorothioate oligonucleotide, ISIS 2105, for induction of an immune response. The specification does not disclose inhalation, opthamalic, intranasal, parenteral, or oral administration of any phosphorothioate oligonucleotide.

The different routes of administration would be accommodated by different types of immune responses. For example, oral administration would be affected by specialized antigen presenting cells that induce tolerance to an antigen rather than an immune response as taught by Smith, et al. (Immunology, 2002. Vol. 106, pages 144-58). Additionally, Staines (Medical Hypotheses, 2008. Vol. 70, pages 137-40) teach that the eye is considered an immune privileged site in that there is a physiologic mechanism which protects it against pathogens and inflammation.

There is insufficient evidence or nexus that would lead the skilled artisan to predict the ability to induce an immune response by inhalation, opthamalic, intranasal, parenteral, or oral administration of any phosphorothioate oligonucleotide. The specification does not teach different phosphorothioate oligonucleotides. The specification does not teach different routes of administration.

In view of the lack of the predictability of the art to which the invention pertains, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for inducing an immune response, commensurate in scope with the claimed invention.

Double Patenting

10. The rejection of claims 26, 28, 29, and 30 as being unpatentable over claims 1-8 of US Patent 6,727,230 (Hutcherson, et al.) in view of US Patent 5356882 (Walker, et al.) is maintained.

The response filed August 14, 2008 has been carefully considered but is deemed not to be persuasive. The response states that applicant's may consider filing a Terminal Disclaimer if some claims are found to be allowable (see response page 9).

In response to this argument, since the claims have not been found to be allowable and a Terminal Disclaimer has not been filed, the rejection is maintained.

Conclusion

11. No claims are allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANNE M. GUSSOW whose telephone number is (571)272-6047. The examiner can normally be reached on Monday - Friday 8:30 am - 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Anne M. Gussow

November 4, 2008

/David J Blanchard/
Primary Examiner, Art Unit 1643